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Pharmacodynamic phMRI with Joint Estimation of the Arterial Drug Input Curve

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This study introduces a refinement to a method for quantifying the sensitivity of multiple brain regions to a drug. Rapid quantitative pharmacodynamic imaging simultaneously estimates pharmacokinetic (PK) and pharmacodynamic (PD) parameters from a region of brain through administration of a drug during fMRI BOLD signal collection. Here we use the fact that the concentration of drug in arterial blood is essentially the same for all regions of the brain to more tightly estimate the time–concentration curve and hence reduce unwanted model flexibility in estimating PD parameters. Furthermore, assuming linear pharmacokinetics, we can appropriately combine responses to the drug across doses. To test this approach, a dopamine D1-like agonist, SKF38393, was administered intravenously to baboons (n = 4) during BOLD-sensitive fMRI. Each subject received four different doses of drug on four different occasions with order randomized. Data from the hypothalamus, midbrain, and striatum were used to estimate the most likely time–concentration curve; the 90% confidence interval for this curve was much tighter than the range of curves when data for each region and dose were considered one at a time. The most likely time–concentration curve was then used as prior information to constrain quantification of drug sensitivity (EC50) voxel-wise throughout the brain. The results support the use of rapid quantitative pharmacological imaging in determining appropriate and effective dosing for brain disorders such as Parkinson's disease as well as for determining arterial drug concentration measurements when this data is not directly available.